



⑫ **EUROPEAN PATENT SPECIFICATION**

④⑤ Date of publication of patent specification :  
**01.09.93 Bulletin 93/35**

⑤① Int. Cl.<sup>6</sup>: **C07D 473/04, C07D 473/06**

②① Application number : **90500126.9**

②② Date of filing : **19.12.90**

⑤④ **Xanthine derivatives.**

③① Priority : **27.12.89 GB 8929208**

④③ Date of publication of application :  
**03.07.91 Bulletin 91/27**

④⑤ Publication of the grant of the patent :  
**01.09.93 Bulletin 93/35**

⑥④ Designated Contracting States :  
**AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

⑤⑥ References cited :  
**EP-A- 0 001 735**

⑦③ Proprietor : **LABORATORIOS ALMIRALL SA**  
**Cardener 68-74**  
**E-08024 Barcelona (ES)**

⑦② Inventor : **Noverola, Armando Vega**  
**Traversera de Dalt, 62-64, 7o, 3o**  
**Barcelona-24 (ES)**  
Inventor : **Soto, Jose Manuel Prieto**  
**Rabassa 46-48, 2o, 2o, Esc. B**  
**Barcelona-24 (ES)**  
Inventor : **Mauri, Jacinto Moragues**  
**Secretario Coloma, 72, 2o, 4o**  
**Barcelona (ES)**  
Inventor : **Gristwood, Robert W.**  
**Calle Granollers 446**  
**San Cugat del Valles, Barcelona (ES)**

⑦④ Representative : **Goldin, Douglas Michael et al**  
**J.A. KEMP & CO. 14, South Square Gray's Inn**  
**London WC1R 5EU (GB)**

**EP 0 435 811 B1**

Note : Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

## Description

This invention relates to new therapeutically useful xanthine derivatives, to processes for their preparation and pharmaceutical compositions containing them.

It is known that cyclic adenosine monophosphate (AMP, a cyclic nucleotide) is an important mediator of cellular function, and when its intracellular concentration is increased eg. via adenylate cyclase stimulation, effects such as smooth muscle relaxation, cardiac stimulation and inhibition of secretory cells are provoked.

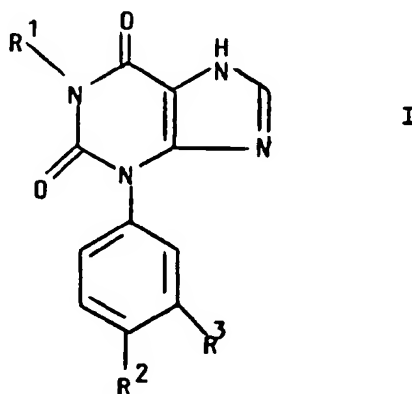
The phosphodiesterases (PDE) are the enzymes responsible for the destruction of cyclic nucleotides and like stimulants of nucleotide cyclases, PDE inhibitors also increase levels of cyclic AMP and are effective as bronchodilators, vasodilators, cardiac stimulants, etc.

Many xanthine derivatives, such as theophylline, have been described as PDE inhibitors, however, its lack of selectivity against the different types of PDE is one reason for the undesirable side effect profile seen with theophylline in man.

There are currently known to be at least 7 different types of PDE enzymes. Inhibition of PDE III (a cyclic guanosine monophosphate inhibited, high affinity cyclic adenosine monophosphate enzyme, see Reeves et al., 1987. Biochem J. 241, 535) increases intracellular cyclic adenosine monophosphate concentrations and effects include a specific cardiac stimulation. Selective inhibition of PDE IV, (a particular cyclic AMP phosphodiesterase, see Reeves et al. 1987) on the other hand increases intracellular cyclic adenosine monophosphate concentrations and produces responses associated with these increases but without directly producing cardiac stimulation. Thus selective PDE IV inhibitors are useful in the treatment of diseases in which the production of cardiac stimulation is not appropriate (eg. asthma).

We have now unexpectedly found that xanthine derivatives with a substituted phenyl group in position 3 and a 3-6 carbon atom chain in position 1, potently inhibit type IV-PDE and are much weaker at inhibiting the type III enzyme, and for this reason they are useful in the treatment of disease without directly producing cardiac stimulation.

The new xanthine derivatives of the present invention are accordingly those compounds of the general formula:



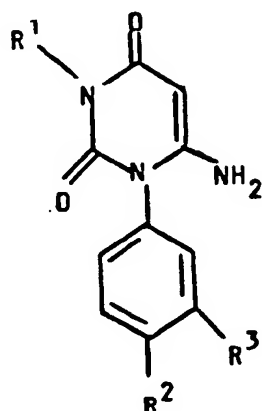
wherein R1 represents a straight or branched chain alkyl, alkenyl or alkynyl group containing from 3 to 6 (preferably 3 or 4) carbon atoms, and R2 and R3 each represent hydrogen or halogen or a methyl, methoxy, nitro or trifluoromethyl group or R2 and R3 form together a methylenedioxy or ethylenedioxy group; with the proviso that R2 and R3 are not both hydrogen, and pharmacologically acceptable salts thereof formed with an alkali metal base or a nitrogen-containing organic base.

Preferred compounds of general formula I are those wherein R1 is a straight chain alkyl group or those wherein R1 represents a n- or isopropyl, n-, iso or tert-butyl or n-hexyl group, R2 and R3 which may be the same or different represent hydrogen or halogen e.g. F, Cl or Br, or a methoxy group or R2 and R3 together represent methylenedioxy. Of outstanding interest are

- 1-n-propyl-3-(4-chlorophenyl)-xanthine,
- 1-n-propyl-3-(3,4-dichlorophenyl)-xanthine,
- 1-n-butyl-3-(3-nitrophenyl)-xanthine,
- 1-n-butyl-3-(3-methoxyphenyl)-xanthine, and
- 1-n-hexyl-3-(3,4-methylenedioxy phenyl)-xanthine.

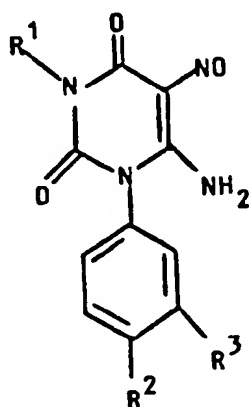
According to a further feature of the present invention, the xanthine derivatives of general formula I can

be prepared from the corresponding 6-aminouracil of the general formula:



II

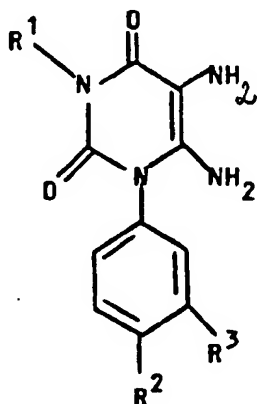
(wherein R1, R2 and R3 are as hereinbefore defined) by nitrosation, preferably with sodium nitrite and formic acid in an excess of formamide, preferably at a temperature of 40°C to 80°C. In the reaction, the corresponding 5-nitroso derivative of general formula III is first formed in the reaction mixture:



III

(wherein R1, R2 and R3 are as hereinbefore defined).

A reducing agent such as sodium dithionite is then slowly added to the reaction mixture, preferably at a temperature of 90°C to 120°C. This reduces the 5-nitroso group to give the corresponding 5,6-diamino derivative of general formula IV:



IV

(wherein R1, R2 and R3 are as hereinbefore defined) which afterwards reacts with the formamide, usually at a temperature of 170°C to 190°C to give the xanthine derivative of general formula I which is then isolated in manner known per se.

By the term "methods known per se" as used in this specification and accompanying claims is meant methods heretofore or used or described in the literature.

An excess of formic acid must be used in the reaction with the 6-aminouracil derivative II and sodium nitrite, and preferably, at least two moles of formic acid are employed per mole of 6-aminouracil derivative.

Although compounds III and IV that are successively formed during the process can be isolated, the preparation of xanthine derivatives of general formula I is preferably carried out in a single step without isolation of the intermediate compounds III and IV.

The 6-aminouracil derivatives of general formula II can be prepared from the corresponding N,N'-disubstituted urea by methods known per se, e.g. V. Papesch and E.F. Schroeder, J. Org. Chem., 16 1879-90 (1951).

The xanthine derivatives of general formula I obtained by the processes described above, can be purified by application of methods known per se, for example by recrystallization from an organic solvent, e. g. methanol, ethanol, isopropanol, tetrahydrofuran, dioxan or ethyl acetate.

The xanthine derivatives of general formula I may be converted into pharmacologically-acceptable salts with alkali metals or nitrogen-containing organic bases whose salts are formed by reaction of the compounds of general formula I with an alkali metal hydroxide or a nitrogen containing organic base using, for example, water, methanol or ethanol as a solvent at a temperature between 40° and 100°C.

The test used to detect PDE IV inhibitory potency and selectivity is based on observations reported by Gristwood and Owen (Effects of rolipram on guinea-pig ventricles in vitro: Evidence of an unexpected synergism with SK&F 94120. Br. J. Pharmacol., 87, 91P, 1985) that in isolated guinea-pig ventricles, selective PDE III inhibitors (eg. SK&F 94120) produce a positive inotropic response whereas selective PDE IV inhibitors (eg. rolipram) have no effect. There is, however, a synergistic interaction between selective PDE III and PDE IV inhibitors in guinea-pig ventricle. Pre-treatment of guinea-pig ventricle with a concentration of a PDE III inhibitor (eg. amrinone) will thus sensitise the preparation to PDE IV inhibitors which, when subsequently administered, will produce a positive inotropic response.

The test procedure is as follows: male guinea-pigs of weight 400-600 g were killed, their hearts were removed and 2 ventricular preparations (ca 1 cm x 1 mm) cut from the right side. There were then mounted in organ baths containing modified Krebs-Henseleit solution of the following composition (mM): NaCl 118; NaHCO<sub>3</sub> 25; Glucose 11; KCl 5.4; CaCl<sub>2</sub> 2.5; NaH<sub>2</sub>PO<sub>4</sub> 1.2 and MgCl<sub>2</sub> 0.8.

The physiological buffer was maintained at 37°C and continually aerated with 95% O<sub>2</sub> / 5% CO<sub>2</sub> v/v. The preparations were placed under 1 g resting tension and electrically stimulated to contract at 1 Hz whilst force of contraction was measured using an isometric force transducer.

Preparations were equilibrated for 60 minutes during which they were washed every 15 minutes with fresh buffer.

A concentration of a selective PDE III inhibitor (eg. amrinone) (producing about a 100% increase in developed tension) was then added to the organ bath of one preparation in order to sensitize it to PDE IV inhibitors. The other was left untreated (to detect PDE III inhibitory activity) and 10 minutes later compounds under test were added to the organ baths in increasing concentrations and responses in both preparations measured as percentage increases in developed tension. Concentrations causing a 50% increase (EC<sub>50</sub>) were calculated.

TABLE 1

5	Compound	Guinea-Pig Non-Sensitized right ventricle strips (EC <sub>50</sub> μM)	Guinea-Pig Sensitized right ventricle strips (EC <sub>50</sub> μM)
10	THEOPHYLLINE	1000	1516
	A	>100	8.9
	B	>100	7
15	1	>100	1.6
	2	>100	0.1
	5	>100	0.9
	9	>100	0.2
20	10	>100	0.4
	12	>100	1.3
	18	>100	0.2
25	20	>100	0.3
	21	>100	1.2
	36	>100	1

30       \*See structures in Table 2

Compound A is 1-methyl-3-phenylxanthine, a known compound.

35       Compound B is 1-propyl-3-phenyl-8-methylxanthine, a known compound.

40       As can be seen in Table 1 the new xanthine derivatives of the present invention are more active and selective for PDE IV relative to PDE III than the xanthine derivative in which R<sup>1</sup> and R<sup>3</sup> are methyl groups (i.e. theophylline) and are more active for PDE IV than the derivatives in which R<sup>3</sup> is an unsubstituted phenyl group (compounds A and B).

45       The compounds of this invention are bronchodilators and have anti-inflammatory and anti-allergic activities and are therefore of use in combatting allergic/inflammatory diseases such as asthma (reversible obstructive airways disease).

50       The compounds of this invention also have vasodilator activity and are therefore of value in combatting angina, hypertension, congestive heart failure and multi infarct dementia. In addition the compounds are of use in combatting such other conditions wherein inhibition of PDE type IV is thought to be beneficial, such as depression, impaired cognition, rheumatic and other inflammatory diseases, stroke, heterograft rejection and other immune related diseases.

      Also included within the scope of the present invention are pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, or a pharmacologically-acceptable salt thereof as hereinbefore mentioned, in association with a pharmaceutically acceptable carrier or diluent. Preferably the compositions are made up in a form suitable for oral, aerosol, rectal or parenteral administration.

55       The pharmaceutically-acceptable carriers or diluents which are admixed with the active compound or compounds or salts of such compounds to form the compositions of this invention are well known per se and the actual excipients used depend inter alia on the intended method of administration of the compositions. Compositions of this invention are preferably adapted for administration per os. In this case, the compositions for

oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations such as a elixirs, syrups or suspensions, all containing one or more compounds of the invention, such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents if desired. Tablets or capsules may conveniently contain between 1 and 50 mg and preferably from 5 to 30 mg of active ingredient or the equivalent amount of a pharmacologically-acceptable salt thereof. The compounds may also be incorporated into pellets coated with appropriate natural or synthetic polymers known in the art to produce sustained release characteristics or incorporated with polymers into tablet form to produce the same characteristics.

The liquid compositions adapted for oral use may be in the form of solutions, suspensions or aerosols. The solutions may be aqueous or aqueous-alcoholic solutions of a soluble compound or salt thereof in association with, for example, sucrose or sorbitol to form a syrup. The suspensions may comprise an insoluble or microencapsulated form of an active compound of the invention in association with water and other acceptable solvents together with a suspending agent or flavouring agent.

Compositions for oral aerosol administration may be in the form of solutions, suspensions or micronized powder, contained in an appropriate inhaler.

Compositions for parenteral injection may be prepared from soluble compounds or salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

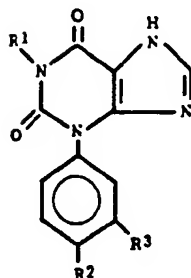
In human therapy, the doses of the xanthine derivatives depend on the desired effect and duration of the treatment; adult doses are generally between 1 mg and 100 mg per day. In general the physician will decide the posology taking into account the age and weight intrinsic to the patient being treated.

The following examples illustrate the invention.

#### 25 EXAMPLE 1

A mixture of 1-(4-chlorophenyl)-3-n-propyl-6-aminouracil (28.0 g; 0.1 mole), formic acid (15.1 ml; 0.4 moles) and sodium nitrite (7 g; 0.1 mole) in formamide (600 ml) was heated to 60°C for 10 minutes. The temperature was then increased to 100°C and sodium dithionite (2.3 g; 0.013 moles) was added over a period of 10 minutes. After addition, the temperature was increased to 190°C, maintained for 30 minutes and the reaction mixture was cooled and extracted with chloroform. The organic solution was extracted with 2N sodium hydroxide aqueous solution, washed with diethyl ether, acidified with 2N hydrochloric acid aqueous solution and extracted with chloroform. The organic extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed in vacuo to give 1-n-propyl-3-(4-chlorophenyl)-xanthine (19.5 g; yield 64.3%). After recrystallization from 90% ethanol, the melting point is 233-234°C.

The xanthine derivatives of general formula I included in Table 2 were prepared according to the process disclosed in this example 1 but with appropriate substitution on the 6-amino uracil reactant.

TABLE 2

Comp. Nr.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Melting Point °C
1	nC <sub>3</sub> H <sub>7</sub>	Cl	H	233-234
2	"	H	Cl	196-198
3	"	F	H	258-259
4	"	H	F	213-214
5	"	Br	H	228-229
6	"	CH <sub>3</sub>	"	227-229
7	"	"	CH <sub>3</sub>	224-226
8	"	OCH <sub>3</sub>	H	203-205
9	"	H	OCH <sub>3</sub>	203-205
10	"	"	NO <sub>2</sub>	224-228
11	"	"	CF <sub>3</sub>	159-161
12	"	Cl	Cl	231-232
13	"	F	F	231-232
14	"	OCH <sub>3</sub>	OCH <sub>3</sub>	248-249
15	"	"	Cl	266-268
16	n-C <sub>4</sub> H <sub>9</sub>	Cl	H	197-198
17	"	H	Cl	191-192
18	"	F	H	246-248
19	"	H	F	172-173
20	"	OCH <sub>3</sub>	H	197-200
21	"	H	OCH <sub>3</sub>	189-190
22	"	"	NO <sub>2</sub>	177-180
23	"	Cl	Cl	206-208
24	"	H	CF <sub>3</sub>	167-168
25	nC <sub>5</sub> H <sub>11</sub>	Cl	H	180-183

TABLE 2 (Continued)

	Comp. Nr.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Melting Point °C
5	26	"	"	Cl	211-212
	27	nC <sub>6</sub> H <sub>13</sub>	"	H	161-163
10	28	"	"	Cl	190-191 (d)
	29	iC <sub>4</sub> H <sub>9</sub>	"	H	218-219
	30	"	"	Cl	218-219
15	31	CH <sub>2</sub> -CH=CH <sub>2</sub>	"	H	242-244
	32	CH <sub>2</sub> -C≡CH	"	"	261-262
	33	n-C <sub>3</sub> H <sub>7</sub>	0-CH <sub>2</sub> -0		225-227
	34	n-C <sub>4</sub> H <sub>9</sub>	0-CH <sub>2</sub> -0		214-216
20	35	n-C <sub>5</sub> H <sub>11</sub>	"		218-219
	36	n-C <sub>6</sub> H <sub>13</sub>	"		167-169
	37	i-C <sub>4</sub> H <sub>9</sub>	"		247-248
25	38	n-C <sub>3</sub> H <sub>7</sub>	0-CH <sub>2</sub> CH <sub>2</sub> -0		222-223
	39	n-C <sub>4</sub> H <sub>9</sub>	"		180-181

30 The following Examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 2

35 100,000 capsules each containing 20 mg of 1-n-propyl-3-(4-chloro- or 3,4-dichlorophenyl)-xanthine (active ingredient) were prepared from the following formulation:

40	1-n-propyl-3-(4-chloro- or 3,4-dichlorophenyl)- xanthine	2 kg
	Lactose monohydrate	11.7 kg
	Corn starch	1 kg
	Colloidal silicon dioxide	0.1 kg
45	Magnesium stearate	0.2 kg

Procedure

50 The above ingredients were sieved through a 60-mesh sieve, then mixed in a suitable mixer and filled into 100,000 gelatine capsules.

EXAMPLE 3

55 1000 bottles of suspension (capacity 150 ml) each containing 150 mg of 1-n-butyl-3-(3-nitrophenyl)-xanthine were prepared as follows:



	1-n-butyl-3-(3-nitrophenyl)-xanthine	150 g
	microcrystalline cellulose	1,500 g
5	sodium carboxymethylcellulose	900 g
	70% sorbitol aqueous solution	33,000 g
	glycerine	4,500 g
	polysorbate 80	400 g
10	sodium methyl p-hydroxybenzoate	240 g
	sodium propyl p-hydroxybenzoate	60 g
	anti-foam silicone	150 g
15	sodium saccharin	300 g
	flavouring q.s.	
	demineralised water q.s.	150 litres

20

Procedure

To a solution of the sodium methyl p-hydroxybenzoate, sodium propyl p-hydroxybenzoate and sodium saccharin in 30 litres of demineralised water, a wetmilled suspension of the sodium carboxymethylcellulose in glycerine was added. After stirring for 1 hour, a suspension of the microcrystalline cellulose in 60 litres of demineralised water was added and then the sorbitol solution, polysorbate 80, 1-n-butyl-3-(3-nitrophenyl)-xanthine and flavouring were successively added with stirring. The volume of the mixture was adjusted to 125 litres with demineralised water and milled through a colloidal mill. Antifoam silicone was added and the suspension made up to volume with demineralised water and filled into 150 ml bottles using an appropriate filling machine.

30

EXAMPLE 4

20,000 bottles of solution (capacity 150 ml) each containing 150 mg of 1-n-butyl-3-(3-methoxyphenyl)-xanthine were prepared as follows:

35

	1-n-butyl-3-(3-methoxyphenyl)-xanthine	3 kg
	ethanol	45 kg
40	70% sorbitol aqueous solution	1,050 kg
	sodium saccharin	3 kg
	sodium carboxymethylcellulose	60 kg
	flavouring q.s.	
45	demineralised water q.s.	3,000 litres

50

Procedure

A solution of the sodium carboxymethylcellulose in 1,000 litres of water and 5 kg of ethanol was added to another solution of the 1-n-butyl-3-(3-methoxyphenyl)-xanthine in 40 kg of ethanol and 500 litres of water at a temperature of 50°C. Then the sorbitol solution, sodium saccharin and flavouring were added and the volume of the mixture was adjusted to 3,000 litres with demineralised water. After filtration, the solution was filled into 150 ml bottles using an appropriate filling machine.

55

**EXAMPLE 5**

10,000 Suppositories each containing 50 mg of 1-n-hexyl-3-(3,4-methylenedioxyphenyl)-xanthine were prepared as follows:

1-n-hexyl-3-(3,4-methylenedioxyphenyl)- xanthine	500 g
theobroma oil	19,500 g

The theobroma oil was melted and the active compound suspended in it. The mixture was then poured into appropriate suppository mould to make 2.0 g suppositories.

**EXAMPLE 6**

8,000 Inhalation-flasks each containing 100 mg of 1-n-hexyl-3-(3,4-methylenedioxyphenyl)-xanthine (active compound) were prepared as follows:

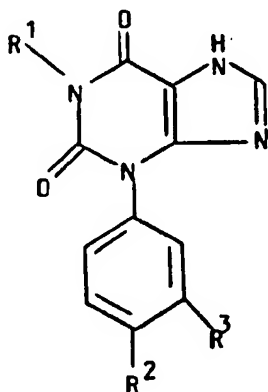
1-n-hexyl-3-(3,4-methylenedioxyphenyl)-xanthine	800 g
sorbitan trioleate	8 g
water q.s.	160 litres
nitrogen q.s. to a pressure of 7-8 kg/cm <sup>2</sup>	

The microcrystalline suspension prepared with these ingredients was introduced in the inhalation-flasks at a volume of 20 ml per flask with a filling machine at a nitrogen pressure of 7-8 kg/cm<sup>2</sup>. The flasks are furnished with an appropriate valve which releases 0.2 ml of suspension in each activation (1 mg of active compound).

**Claims**

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

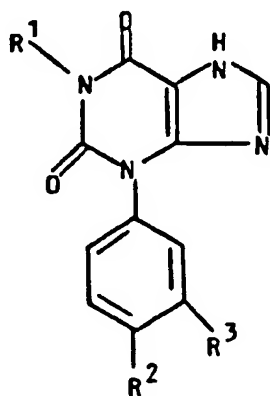
1. A compound of the general formula:



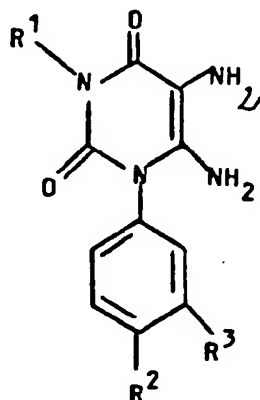
wherein R<sup>1</sup> represents a straight or branched chain alkyl, alkenyl or alkynyl group of 3-6 carbon atoms, and R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, each represent hydrogen or halogen or a methyl, methoxy, nitro or trifluoromethyl group or R<sup>2</sup> and R<sup>3</sup> together form a methylenedioxy or ethylenedioxy group; with the proviso that R<sup>2</sup> and R<sup>3</sup> are not both hydrogen; and pharmacologically acceptable salts

thereof with an alkali metal base or a nitrogen containing organic base.

2. A compound according to claim 1 wherein R<sup>1</sup> is an n-propyl, iso-propyl, n-butyl, iso-butyl, tert.butyl or n-hexyl group.
3. A compound according to claim 1 or 2 wherein R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, each represent H, F, Cl, Br, or methoxy or R<sup>2</sup> and R<sup>3</sup> together represent methylenedioxy.
4. A compound according to claim 1 which is  
 1-n-propyl-3-(4-chlorophenyl)-xanthine,  
 1-n-propyl-3-(3,4-dichlorophenyl)-xanthine,  
 1-n-butyl-3-(3-nitrophenyl)-xanthine,  
 1-n-butyl-3-(3-methoxyphenyl)-xanthine  
 or 1-n-hexyl-3-(3,4-methylenedioxyphenyl)-xanthine.
5. A process for preparing a compound of the general formula:



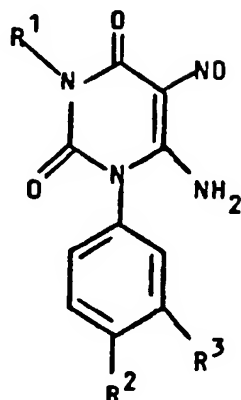
wherein R<sup>1</sup> represents a straight or branched chain alkyl, alkenyl or alkynyl group of 3-6 carbon atoms, and R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, each represent hydrogen or halogen or a methyl, methoxy, nitro or trifluoromethyl group or R<sup>2</sup> and R<sup>3</sup> together form a methylenedioxy or ethylenedioxy group; with the proviso that R<sup>2</sup> and R<sup>3</sup> are not both hydrogen; and pharmacologically acceptable salts thereof with an alkali metal base or a nitrogen containing organic base, which comprises reacting a 5,6-diamine of the general formula:



where R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, with formamide.

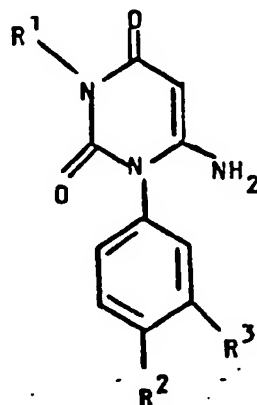
6. A process according to claim 5 wherein the 5,6-diamine is prepared by reducing a 6-amino-5-nitroso com-

pound of the general formula:



III

7. A process according to claim 6 wherein the 6-amino-5-nitroso compound is prepared by nitrosating a 6-amino-uracil of the general formula:

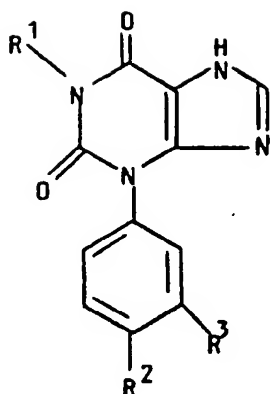


II

8. A process according to claims 5-7 wherein the 6-amino-5-nitroso compound and the 5,6-diamine are formed in situ.
9. A process according to claim 8 wherein the 6-amino-uracil of formula II is reacted with sodium nitrite and formic acid in an excess of formamide and sodium dithionite added to the reaction mixture to reduce the resulting 6-amino-5-nitroso compound.
10. A process according to any one of claims 5-9 wherein the resulting xanthine of formula I is isolated in the form of a salt with an alkali metal or nitrogen containing organic base.
11. A pharmaceutical composition comprising a xanthine of the general formula I or salt thereof as defined in any one of claims 1-4 together with a pharmaceutically acceptable carrier or diluent.
12. A xanthine or salt thereof as defined in any one of claims 1-4 for use in a method of treatment of the human or animal body by therapy.

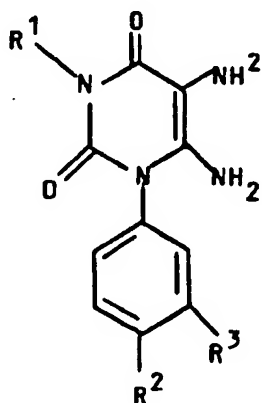
**Claims for the following Contracting States :ES, GR**

1. A process for preparing a compound of the general formula:



I

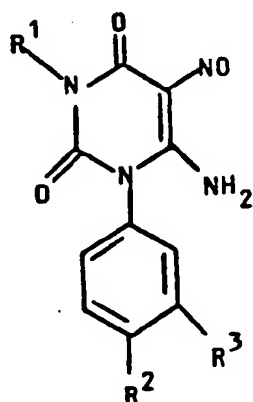
wherein R<sup>1</sup> represents a straight or branched chain alkyl, alkenyl or alkynyl group of 3-6 carbon atoms, and R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, each represent hydrogen or halogen or a methyl, methoxy, nitro or trifluoromethyl group or R<sup>2</sup> and R<sup>3</sup> together form a methylenedioxy or ethylenedioxy group; with the proviso that R<sup>2</sup> and R<sup>3</sup> are not both hydrogen; and pharmacologically acceptable salts thereof with an alkali metal base or a nitrogen containing organic base, which comprises reacting a 5,6-



IV

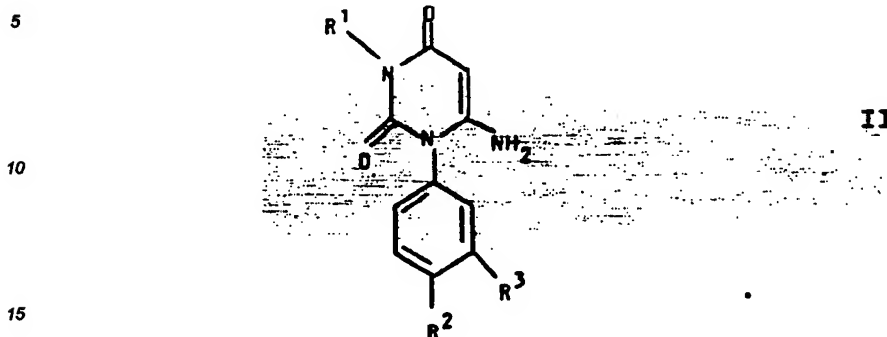
where R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, with formamide.

2. A process according to claim 1 wherein the 5,6-diamine is prepared by reducing a 6-amino-5-nitroso compound of the general formula:



III

3. A process according to claim 2 wherein the 6-amino-5-nitroso compound is prepared by nitrosating a 6-amino-uracil of the general formula:



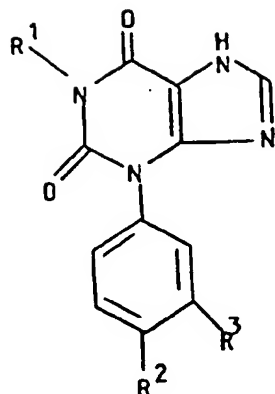
- 20
- 25
- 30
- 35
- 40
4. A process according to claims 1-3 wherein the 6-amino-5-nitroso compound and the 5,6-diamine are formed in situ.
  5. A process according to claim 4 wherein the 6-amino-uracil of formula II is reacted with sodium nitrite and formic acid in an excess of formamide and sodium dithionite added to the reaction mixture to reduce the resulting 6-amino-5-nitroso compound.
  6. A process according to any one of the preceding claims wherein the resulting xanthine of formula I is isolated in the form of a salt with an alkali metal or nitrogen containing organic base.
  7. A process according to any one of the preceding claims wherein R<sup>1</sup> is an n-propyl, iso-propyl, n-butyl, iso-butyl, tert.butyl or n-hexyl group.
  8. A process according to any one of the preceding claims wherein R<sup>2</sup> and R<sup>3</sup>, which may be the same or different, each represent H, F, Cl, Br, or methoxy or R<sup>2</sup> and R<sup>3</sup> together represent methylenedioxy.
  9. A process according to any one of the preceding claims in which  
 1-n-propyl-3-(4-chlorophenyl)-xanthine,  
 1-n-propyl-3-(3,4-dichlorophenyl)-xanthine,  
 1-n-butyl-3-(3-nitrophenyl)-xanthine,  
 1-n-butyl-3-(3-methoxyphenyl)-xanthine  
 or 1-n-hexyl-3-(3,4-methylenedioxyphenyl)-xanthine is prepared.
  10. A process for preparing a pharmaceutical composition which comprises formulating a xanthine of the general formula I or salt thereof as defined in any one of claims 1 or 7-9 with a pharmaceutically acceptable carrier or diluent.

#### 45 Patentansprüche

Patentanprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

- 50 1. Verbindung der allgemeinen Formel

55



I

5

10

15

20

worin R¹ für einen gerad- oder verzweigt-kettigen Alkyl-, Alkenyl- oder Alkynylrest mit 3 bis 6 Kohlenstoffatomen steht, und R² und R³, die gleich oder verschieden sein können, jeweils für ein Wasserstoff- oder Halogenatom oder eine Methyl-, Methoxy-, Nitro- oder Trifluormethylgruppe stehen, oder R² und R³ zusammen eine Methylendioxy- oder Ethylendioxygruppe bilden, mit der Maßgabe, daß R² und R³ nicht beide für ein Wasserstoffatom stehen, und pharmakologisch annehmbare Salze davon mit einer Alkalimetallbase oder einer stickstoffhaltigen organischen Base.

25

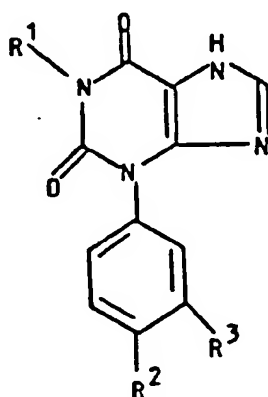
30

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß R¹ für eine n-Propyl-, Isopropyl-, n-Butyl-, Isobutyl-, tert.-Butyl- oder n-Hexylgruppe steht.
3. Verbindung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß R² und R³, die gleich oder verschieden sein können, jeweils für H, F, Cl, Br oder eine Methoxygruppe stehen, oder R² und R³ zusammen eine Methylendioxygruppe bilden.
4. Verbindung nach Anspruch 1, nämlich 1-n-Propyl-3-(4-chlorphenyl)-xanthin, 1-n-Propyl-3-(3,4-dichlorphenyl)-xanthin, 1-n-Butyl-3-(3-nitrophenyl)-xanthin, 1-n-Butyl-3-(3-methoxyphenyl)-xanthin oder 1-n-Hexyl-3-(3,4-methylenedioxyphenyl)-xanthin.
5. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel

35

40

45

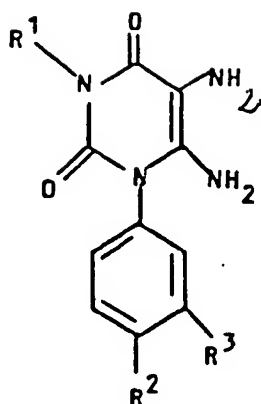


I

50

55

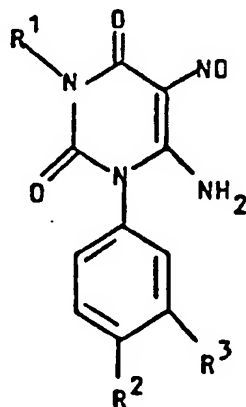
worin R¹ für einen gerad- oder verzweigt-kettigen Alkyl-, Alkenyl- oder Alkynylrest mit 3 bis 6 Kohlenstoffatomen steht, und R² und R³, die gleich oder verschieden sein können, jeweils für ein Wasserstoff- oder Halogenatom oder eine Methyl-, Methoxy-, Nitro- oder Trifluormethylgruppe stehen, oder R² und R³ zusammen eine Methylendioxy- oder Ethylendioxygruppe bilden, mit der Maßgabe, daß R² und R³ nicht beide für ein Wasserstoffatom stehen, und pharmakologisch annehmbarer Salze davon mit einer Alkalimetallbase oder einer stickstoffhaltigen organischen Base, dadurch gekennzeichnet, daß man ein 5,6-Di-amin der allgemeinen Formel



IV

worin R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> wie vorstehend definiert sind, mit Formamid umgesetzt.

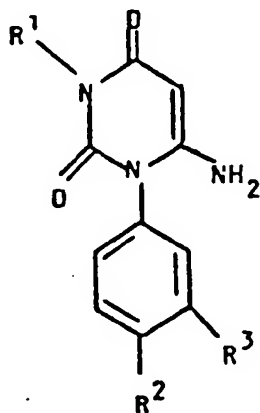
6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das 5,6-Diamin durch Reduktion einer 6-Amino-5-nitroso-Verbindung der allgemeinen Formel



III

hergestellt wird.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß die 6-Amino-5-nitroso-Verbindung durch Nitrosieren von 6-Aminouracil der allgemeinen Formel



II

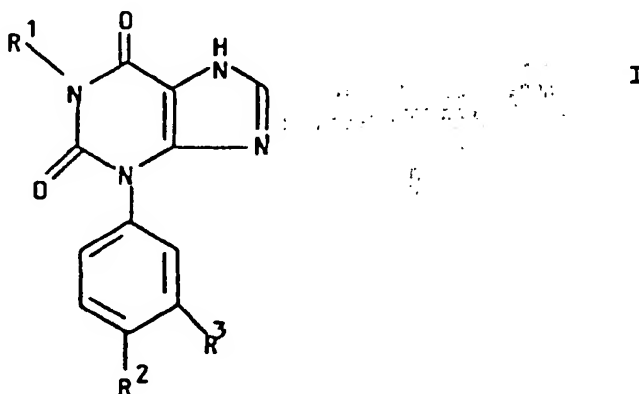


hergestellt wird.

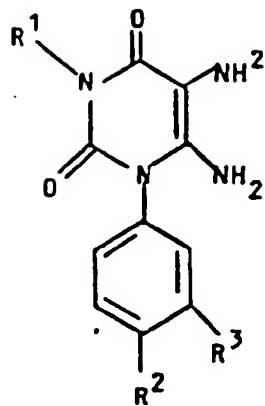
8. Verfahren nach den Ansprüchen 5 bis 7, dadurch gekennzeichnet, daß die 6-Amino-5-nitroso-Verbindung und das 5,6-Diamin in situ gebildet werden.
9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß das 6-Aminouracil der Formel II mit Natriumnitrit und Ameisensäure in einem Überschuß an Formamid umgesetzt wird, und Natriumdithionit dem Reaktionsgemisch zur Reduktion der so erhaltenen 6-Amino-5-nitroso-Verbindung zugesetzt wird.
10. Verfahren nach einem der Ansprüche 5 bis 9, dadurch gekennzeichnet, daß das so erhaltene Xanthin der Formel I in Form eines Salzes mit einem Alkalimetall oder einer stickstoffhaltigen organischen Base isoliert wird.
11. Pharmazeutisches Präparat, umfassend ein Xanthin der allgemeinen Formel I oder ein Salz davon, wie in einem der Ansprüche 1 bis 4 definiert, zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.
12. Xanthin oder ein Salz davon, wie in einem der Ansprüche 1 bis 4 definiert, zur Verwendung bei einem Verfahren zur therapeutischen Behandlung des menschlichen oder tierischen Körpers.

**Patentansprüche für folgende Vertragsstaaten : ES, GR**

1. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel



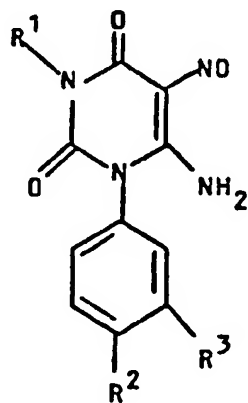
worin R<sup>1</sup> für einen gerad- oder verzweigt-kettigen Alkyl-, Alkenyl- oder Alkynylrest mit 3 bis 6 Kohlenstoffatomen steht, und R<sup>2</sup> und R<sup>3</sup>, die gleich oder verschieden sein können, jeweils für ein Wasserstoff- oder Halogenatom oder eine Methyl-, Methoxy-, Nitro- oder Trifluormethylgruppe stehen, oder R<sup>2</sup> und R<sup>3</sup> zusammen eine Methylendioxy- oder Ethylendioxygruppe bilden, mit der Maßgabe, daß R<sup>2</sup> und R<sup>3</sup> nicht beide für ein Wasserstoffatom stehen, und pharmakologisch annehmbare Salze davon mit einer Alkalimetallbase oder einer stickstoffhaltigen organischen Base, dadurch gekennzeichnet, daß man ein 5,6-Diamin der allgemeinen Formel



IV

worin R<sup>1</sup>, R<sup>2</sup> und R<sup>3</sup> wie vorstehend definiert sind, mit Formamid umgesetzt.

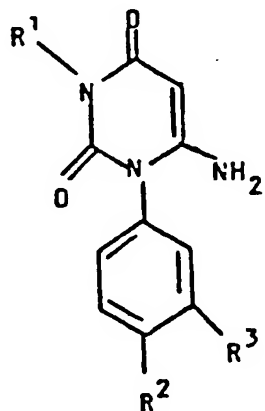
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das 5,6-Diamin durch Reduktion einer 6-Amino-5-nitroso-Verbindung der allgemeinen Formel



III

hergestellt wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die 6-Amino-5-nitroso-Verbindung durch Nitrosieren von 6-Aminouracil der allgemeinen Formel



II

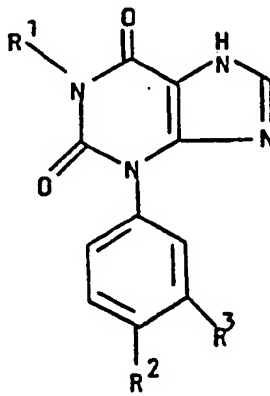
hergestellt wird.

4. Verfahren nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß die 6-Amino-5-nitroso-Verbindung und das 5,6-Diamin in situ gebildet werden.
5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das 6-Aminouracil der Formel II mit Natriumnitrit und Ameisensäure in einem Überschuß an Formamid umgesetzt wird, und Natriumdithionit dem Reaktionsgemisch zur Reduktion der so erhaltenen 6-Amino-5-nitroso-Verbindung zugesetzt wird.
6. Verfahren nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß das so erhaltene Xanthin der Formel I in Form eines Salzes mit einem Alkalimetall oder einer stickstoffhaltigen organischen Base isoliert wird.
7. Verfahren nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß R<sup>1</sup> für eine n-Propyl-, Isopropyl-, n-Butyl-, Isobutyl-, tert.-Butyl- oder n-Hexylgruppe steht.
8. Verfahren nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß R<sup>2</sup> und R<sup>3</sup>, die gleich oder verschieden sein können, jeweils für H, F, Cl, Br oder eine Methoxygruppe stehen, oder R<sup>2</sup> und R<sup>3</sup> zusammen eine Methylendioxygruppe bilden.
9. Verfahren nach einem der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß 1-n-Propyl-3-(4-chlorphenyl)-xanthin, 1-n-Propyl-3-(3,4-dichlorphenyl)-xanthin, 1-n-Butyl-3-(3-nitrophenyl)-xanthin, 1-n-Butyl-3-(3-methoxyphenyl)-xanthin oder 1-n-Hexyl-3-(3,4-methylendioxyphenyl)-xanthin hergestellt werden.
10. Verfahren zur Herstellung eines pharmazeutischen Präparats, dadurch gekennzeichnet, daß man ein Xanthin der allgemeinen Formel I oder ein Salz davon, wie in einem der Ansprüche 1 oder 7 bis 9 definiert, mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel formuliert.

### Revendications

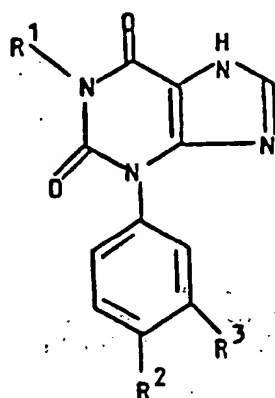
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule générale :



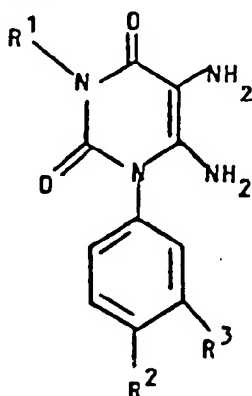
dans laquelle R<sup>1</sup> représente un groupe alkyle, alcényle ou alcynyle, à 3-6 atomes de carbone, à chaîne droite ou ramifiée, et R<sup>2</sup> et R<sup>3</sup>, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou d'halogène ou un groupe méthyle, méthoxy, nitro ou trifluorométhyle, ou R<sup>2</sup> et R<sup>3</sup> forment ensemble un groupe méthylendioxy ou éthylendioxy ; étant entendu que R<sup>2</sup> et R<sup>3</sup> ne représentent pas en même temps un atome d'hydrogène ; et leurs sels pharmacologiquement acceptables avec une base de métal alcalin ou une base organique azotée.

2. Composé selon la revendication 1, dans lequel R<sup>1</sup> représente un groupe n-propyle, iso-propyle, n-butyle, iso-butyle, tert.-butyle ou n-hexyle.
3. Composé selon la revendication 1 ou 2, dans lequel R<sup>2</sup> et R<sup>3</sup>, qui peuvent être identiques ou différents, représentent chacun un atome de H, F, Cl, Br ou un groupe méthoxy, ou R<sup>2</sup> et R<sup>3</sup> représentent ensemble un groupe méthylènedioxy.
4. Composé selon la revendication 1, qui est :  
la 1-n-propyl-3-(4-chlorophényl)-xanthine,  
la 1-n-propyl-3-(3,4-dichlorophényl)-xanthine,  
la 1-n-butyl-3-(3-nitrophényl)-xanthine,  
la 1-n-butyl-3-(3-méthoxyphényl)-xanthine, ou  
la 1-n-hexyl-3-(3,4-méthylènedioxyphényl)-xanthine.
5. Procédé de préparation d'un composé de formule générale :



I

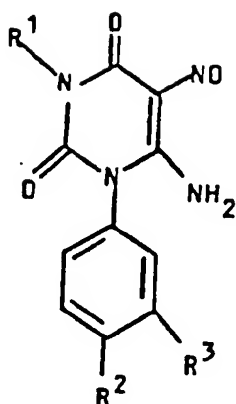
dans laquelle R<sup>1</sup> représente un groupe alkyle, alcényle ou alcynyle, à 3-6 atomes de carbone, à chaîne droite ou ramifiée, et R<sup>2</sup> et R<sup>3</sup>, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou d'halogène ou un groupe méthyle, méthoxy, nitro ou trifluorométhyle, ou R<sup>2</sup> et R<sup>3</sup> forment ensemble un groupe méthylènedioxy ou éthylènedioxy ; étant entendu que R<sup>2</sup> et R<sup>3</sup> ne représentent pas en même temps un atome d'hydrogène ; et leurs sels pharmacologiquement acceptables avec une base de métal alcalin ou une base organique azotée, comprenant l'étape consistant à faire réagir une 5,6-diamine de formule générale :



IV

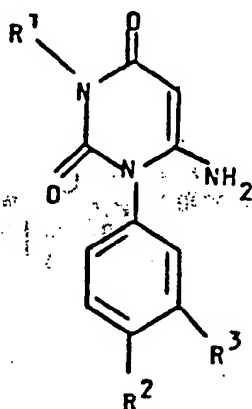
dans laquelle R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> sont définis comme ci-dessus, avec le formamide.

6. Procédé selon la revendication 5, dans lequel la 5, 6-diamine est préparée par réduction d'un composé 6-amino-5-nitroso de formule générale :



III

7. Procédé selon la revendication 6, dans lequel le composé 6-amino-5-nitroso est préparé par nitrosation d'un 6-amino-uracile de formule générale :

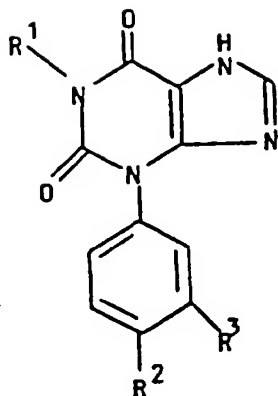


II

8. Procédé selon les revendications 5-7, dans lequel le composé 6-amino-5-nitroso et la 5,6-diamine sont formés in situ.
9. Procédé selon la revendication 8, dans lequel on fait réagir le 6-amino-uracile de formule II avec le nitrite de sodium et l'acide formique, au sein d'une quantité en excès de formamide, et l'on ajoute au mélange réactionnel du dithionite de sodium pour réduire le composé 6-amino-5-nitroso résultant.
10. Procédé selon l'une quelconque des revendications 5-9, dans lequel on isole la xanthine de formule I obtenue sous la forme d'un sel formé avec un métal alcalin ou une base organique azotée.
11. Composition pharmaceutique comprenant une xanthine de formule générale I ou un de ses sels, telle que définie dans l'une quelconque des revendications 1-4, conjointement avec un véhicule ou un diluant pharmaceutiquement acceptable.
12. Xanthine ou un des ses sels, selon l'une quelconque des revendications 1-4, destinée à être utilisée dans une méthode de traitement thérapeutique du corps humain ou animal.

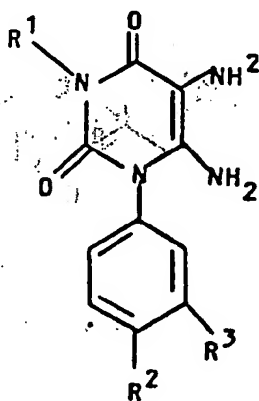
**Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé de préparation d'un composé de formule générale :



I

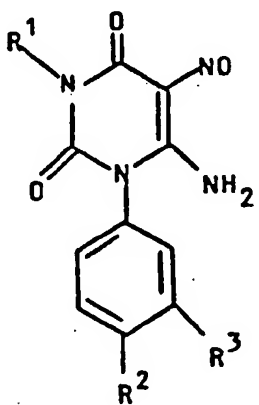
dans laquelle R<sup>1</sup> représente un groupe alkyle, alcényle ou alcynyle, à 3-6 atomes de carbone, à chaîne droite ou ramifiée, et R<sup>2</sup> et R<sup>3</sup>, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou d'halogène ou un groupe méthyle, méthoxy, nitro ou trifluorométhyle, ou R<sup>2</sup> et R<sup>3</sup> forment ensemble un groupe méthylènedioxy ou éthylènedioxy ; étant entendu que R<sup>2</sup> et R<sup>3</sup> ne représentent pas en même temps un atome d'hydrogène ; et leurs sels pharmacologiquement acceptables avec une base de métal alcalin ou une base organique azotée, comprenant l'étape consistant à faire réagir une 5,6-diamine de formule générale :



IV

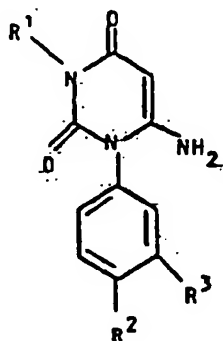
dans laquelle R<sup>1</sup>, R<sup>2</sup> et R<sup>3</sup> sont définis comme ci-dessus, avec le formamide.

2. Procédé selon la revendication 1, dans lequel la 5,6-diamine est préparée par réduction d'un composé 6-amino-5-nitroso de formule générale :



III

3. Procédé selon la revendication 2, dans lequel le composé 6-amino-5-nitroso est préparé par nitrosation d'un 6-amino-uracile de formule générale :



4. Procédé selon les revendications 1-3, dans lequel le composé 6-amino-5-nitroso et la 5,6-diamine sont formés in situ.
5. Procédé selon la revendication 4, dans lequel on fait réagir le 6-amino-uracile de formule II avec le nitrite de sodium et l'acide formique, au sein d'une quantité en excès de formamide, et l'on ajoute au mélange réactionnel du dithionite de sodium pour réduire le composé 6-amino-5-nitroso résultant.
6. Procédé selon l'une quelconque des revendications précédentes, dans lequel on isole la xanthine de formule I obtenue sous la forme d'un sel formé avec un métal alcalin ou une base organique azotée.
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel R<sup>1</sup> représente un groupe n-propyle, isopropyle, n-butyle, iso-butyle, tert.-butyle ou n-hexyle.
8. Procédé selon l'une quelconque des revendications précédentes, dans lequel R<sup>2</sup> et R<sup>3</sup>, qui peuvent être identiques ou différents, représentent chacun un atome de H, F, Cl, Br ou un groupe méthoxy, ou R<sup>2</sup> et R<sup>3</sup> représentent ensemble un groupe méthylènedioxy.
9. Procédé selon l'une quelconque des revendications précédentes, dans lequel on prépare :  
la 1-n-propyl-3-(4-chlorophényl)-xanthine,  
la 1-n-propyl-3-(3,4-dichlorophényl)-xanthine,  
la 1-n-butyl-3-(3-nitrophényl)-xanthine,  
la 1-n-butyl-3-(3-méthoxyphényl)-xanthine, ou  
la 1-n-hexyl-3-(3,4-méthylènedioxyphényl)-xanthine.
10. Procédé de préparation d'une composition pharmaceutique consistant à mélanger une xanthine de formule générale I ou un de ses sels, comme défini dans l'une quelconque des revendications 1 ou 7-9, avec un véhicule ou un diluant pharmaceutiquement acceptable.